IN THE SPECIFICATION:

Please replace paragraph number **[0001]** with the following rewritten paragraph:

[0001] This application claims the benefit of U.S. Provisional Application No. 60/424,428 filed November 6, ~~2002;~~ 2002, which is incorporated herein by reference.

Please replace paragraph number **[0005]** with the following rewritten paragraph:

[0005] Solid implant drug delivery systems containing a drug incorporated in thermoplastic or thermosetting biodegradable polymers have been widely used successfully. Such implants have to be inserted into the body through an incision which is sometimes larger than desired by the medical profession and occasionally lead to a reluctance of the patients to accept such an implant or drug delivery system. The following ~~patents~~ U.S. Patent Nos. 5,456,679; 5,336,057; 5,308,348; 5,279,608; 5,234,693; 5,234,692; 5,209,746; 5,151,093; 5,137,727; 5,112,614; 5,085,866; 5,059,423; 5,057,318; 4,865,845; 4,008,719; 3,987,790 and 3,797,492 are believed to be representative of such drug delivery systems and are incorporated herein by reference. These patents disclose reservoir devices, osmotic delivery devices and pulsatile delivery devices for delivering beneficial agents.

Please replace paragraph number **[0006]** with the following rewritten paragraph:

[0006] Injecting drug delivery systems as small particles, microspheres, or microcapsules avoids the incision needed to implant drug delivery systems. However, these materials do not always satisfy the demand for a biodegradable implant. These materials are particulate in nature, do not form a continuous film or solid implant with the structural integrity needed for certain prostheses, the particles tend to aggregate and thus their behavior is hard to predict. When inserted into certain body ~~cavities~~ cavities, such as a mouth, a periodontal pocket, the eye, or the ~~vagina~~ vagina, where there is considerable fluid flow, these small particles, microspheres, or microcapsules are poorly retained because of their small size and discontinuous nature. Further, if there are complications, removal of microcapsule or small-particle systems

from the body without extensive surgical intervention is considerably more difficult than with solid implants. Additionally, manufacture, storage and injectability of microspheres or microcapsules prepared from these polymers and containing drugs for release into the body present problems.

Please replace paragraph number [0007] with the following rewritten paragraph:

[0007] The art has developed various drug delivery systems in response to the aforementioned challenges. The following ~~patents~~ U.S. Patent Nos. 6,432,438; 5,990,194; 5,780,044; 5,733,950; 5,620,700; 5,599,552; 5,556,905; 5,278,201; 5,242,910 and 4,938,763; and PCT publications WO 98/27962; WO 02/00137 and WO 02/058670 are believed to be representative and are incorporated herein by reference. See also Jain, R. et al., *"Controlled drug delivery by biodegradable poly(ester) devices: different preparative approaches"*, Drug Dev. Ind. Pharm., 24(8): 703-727, 1998; Eliaz, R.E. and Kost, J., *"Characterization of a polymeric PLGA-injectable implant ~~deliver~~ delivery system for the controlled release of proteins"*, J. Biomed. Master Res., 50(3): 388-396, 2000; and Jain, R. A., *"The manufacturing techniques of various drug loaded biodegradable poly(lactide-co-glycolide) (PLGA) devices"*, Biomaterials, 21(23): 2475-90, 2000. These patents and publications disclose polymer compositions for injectable implants using solvents and/or plasticizers.

Please replace paragraph number [0008] with the following rewritten paragraph:

[0008] Previously described polymer compositions for injectable implants have used solvent/plasticizers that are very or relatively soluble in aqueous body fluids to promote rapid solidification of the polymer at the implant site and promote diffusion of drug from the implant. Rapid migration of water into such polymeric implants utilizing water soluble polymer solvents when the implants are placed in the body and exposed to aqueous body fluids presents a serious problem. The rapid water uptake often results in implants having pore structures that are ~~non-~~ nonhomogeneous in size and shape. Typically, the surface pores take on a finger-like pore structure extending for as much as one-third of a millimeter or more from the implant surface

into the implant, and such finger-like pores are open at the surface of the implant to the environment of use. The internal pores tend to be smaller and less accessible to the fluids present in the environment of use. The rapid water uptake characteristic often results in uncontrolled release of beneficial agent that is manifested by an initial, rapid release of beneficial agent from the polymer composition, corresponding to a "burst" of beneficial agent being released from the implant. The burst often results in a substantial portion of the beneficial agent, if not all, being released in a very short time, e.g., hours or 1-2 days. Such an effect can be unacceptable, particularly in those circumstances where a controlled delivery is desired, i.e., delivery of beneficial agent in a controlled manner over a period of greater than or equal to a month or up to one year, or where there is a narrow therapeutic window and release of excess beneficial agent can result in adverse consequences to the subject being treated, or where it is necessary to mimic the naturally-occurring daily profile of beneficial agents, such as hormones and the like, in the body of the subject being treated.

Please replace paragraph number **[0011]** with the following rewritten paragraph:

[0011] Various approaches to control burst and modulate and stabilize the delivery of the beneficial agent have been described. The following ~~patents~~ U.S. Patent Nos. 6,130,200; 5,990,194; 5,780,044; 5,733,950; 5,656,297; 5,654,010; 4,985,404 and 4,853,218 and PCT publication WO 98/27962 are believed to be representative and are incorporated herein by reference. Notwithstanding some success, those methods have not been entirely satisfactory for the large number of beneficial agents that would be effectively delivered ~~by~~ by an implant.

Please replace paragraph number **[0012]** with the following rewritten paragraph:

[0012] The present invention provides a method and an injectable depot gel composition for systemic and local delivery of a beneficial agent to a subject over a prolonged duration of time. In particular, the invention provides controlled release of the beneficial agent to the subject being treated, the release being controlled over a period from about, equal to or greater than two weeks or up to one year after administration, ~~i.e.~~ i.e., from about two weeks to

about twelve months after ~~adminsitration,~~ administration, preferably over a period equal to or greater than one month after administration or preferably over a period from about one month to about twelve months after administration; more preferably over a period equal to or greater than 2 months after administration, preferably over a period equal to or greater than 3 months after administration, preferably over a period of about 3 months to about 9 months after administration, preferably over a period of about 3 months to about 6 months after administration, even more preferably over a period of up to about 3 months, up to about 4 months, up to about 5 ~~months;~~ months and up to about 6 months after administration. A single administration of the injectable depot gel composition provides longer sustained release of active agents over a prolonged duration of time, thus reducing the frequency of administration and improving patient compliance. Additionally, the invention provides a method of preparing the injectable depot gel composition.

Please replace paragraph number **[0013]** with the following rewritten paragraph:

[0013] In one aspect, the invention pertains to an injectable depot composition for sustained delivery of a beneficial agent to a subject in a controlled manner over a predetermined duration of time after administration ~~comprising~~ comprising:

(a) a viscous gel formulation comprising:

(1) a bioerodible, biocompatible polymer, wherein the polymer is a lactic acid-based polymer; and

(2) a solvent having a miscibility in water of less than or equal to 7 wt.% at 25° C, in an amount effective to plasticize the polymer and form a gel therewith; and

(b) a beneficial agent dissolved or dispersed in the gel;

wherein ~~said~~ the beneficial agent is delivered over a duration equal to or greater than one month. Preferably, the polymer is a copolymer of lactic acid and glycolic acid, having a comonomer ratio (an L/G ratio) of about 50:50 to about 100:0; and a molecular weight ranging from about 3,000 to about 120,000.

Please replace paragraph number [0014] with the following rewritten paragraph:

[0014] In another aspect, the invention pertains to an injectable depot composition for sustained delivery of a beneficial agent to a subject in a controlled manner over a predetermined duration of time after administration ~~comprising~~ comprising:

(a) a viscous gel formulation comprising:

(1) a bioerodible, biocompatible polymer, wherein the polymer is a lactic acid-based polymer; and

(2) a solvent having a miscibility in water of less than or equal to 7 wt.% at 25° C, in an amount effective to plasticize the polymer and form a gel therewith; and

(b) a beneficial agent dissolved or dispersed in the gel;

wherein ~~said~~ the beneficial agent is delivered over a duration equal to or greater than one month. Preferably, the polymer is a copolymer of lactic acid and a caprolactone-based polymer including caprolactone (CL), having a comonomer ratio (an L/CL ratio) of about 25:75 to about 75:25; and a molecular weight ranging from about 3,000 to about 120,000.

Please replace paragraph number [0015] with the following rewritten paragraph:

[0015] In another aspect, the invention pertains to an injectable depot composition for sustained systemic delivery of a beneficial agent to a subject in a controlled manner over a duration equal to or greater than one month after administration ~~comprising~~ comprising: (a) a viscous gel formulation comprising: (1) a bioerodible, biocompatible polymer, wherein the polymer is a lactic acid-based polymer; and (2) a solvent having a miscibility in water of less than or equal to 7 wt.% at 25° C, in an amount effective to plasticize the polymer and form a gel therewith; and (b) a beneficial agent dissolved or dispersed in the gel.

Please replace paragraph number [0016] with the following rewritten paragraph:

[0016] In an additional aspect, the invention pertains to an injectable depot composition for sustained delivery of a beneficial agent to a subject in a controlled manner over a predetermined duration of time after administration ~~comprising~~ comprising: (a) a viscous gel

formulation comprising: (1) a bioerodible, biocompatible polymer, wherein the polymer is a lactic acid-based polymer; and (2) a solvent having a miscibility in water of less than or equal to 7 wt.% at 25° C, in an amount effective to plasticize the polymer and form a gel therewith; and (b) a beneficial agent dissolved or dispersed in the gel; wherein the beneficial agent is delivered systemically in a controlled manner over a duration equal to or greater than one month after administration.

Please replace paragraph number **[0017]** with the following rewritten paragraph:

[0017] In another aspect, the invention pertains to an injectable depot composition sustained local delivery of a beneficial agent to a subject in a controlled manner over a duration equal to or greater than one month after administration ~~comprising~~ comprising: (a) a viscous gel formulation comprising: (1) a bioerodible, biocompatible polymer, wherein the polymer is a lactic acid-based polymer; and (2) a solvent having a miscibility in water of less than or equal to 7 wt.% at 25° C, in an amount effective to plasticize the polymer and form a gel therewith; and (b) a beneficial agent dissolved or dispersed in the gel.

Please replace paragraph number **[0018]** with the following rewritten paragraph:

[0018] In an additional aspect, the invention pertains to an injectable depot composition for sustained delivery of a beneficial agent to a subject in a controlled manner over a predetermined duration of time after administration ~~comprising~~ comprising: (a) a viscous gel formulation comprising: (1) a bioerodible, biocompatible polymer, wherein the polymer is a lactic acid-based polymer; and (2) a solvent having a miscibility in water of less than or equal to 7 wt.% at 25° C, in an amount effective to plasticize the polymer and form a gel therewith; and (b) a beneficial agent dissolved or dispersed in the gel; wherein the beneficial agent is delivered locally in a controlled manner over a duration equal to or greater than one month after administration.

Please replace paragraph number **[0022]** with the following rewritten paragraph:

[0022] In preferred embodiments, the solvent is selected from the aromatic alcohol, lower alkyl and aralkyl esters of aryl acids; aryl, aralkyl and lower alkyl ketones; and lower alkyl esters of citric acid. Preferably, the solvent is selected from benzyl alcohol, benzyl benzoate and ethyl benzoate. In preferred embodiments, the composition is free of solvents having a miscibility in water that is greater than 7 wt.% at 25° C. Preferably the solvent has a miscibility in water of less than 7 wt.%, more preferably less than 5~~-wt%,~~ wt.%, and even more preferably less than 3~~-wt%~~ wt.%.

Please replace paragraph number **[0024]** with the following rewritten paragraph:

[0024] In additional aspects, the invention pertains to a kit for sustained delivery administration ~~of for sustained delivery~~ of a beneficial agent to a subject in a controlled manner over a predetermined duration of time after administration comprising:

(a) a bioerodible, biocompatible polymer, wherein the polymer is a lactic acid-based polymer;

(b) a solvent having a miscibility in water of less than or equal to 7 wt.% at 25° C, in an amount effective to plasticize the polymer and form a gel therewith;

(c) a beneficial agent dissolved or dispersed in the gel; and optionally, one or more of the following:

(d) an emulsifying agent;

(e) a pore former;

(f) a solubility modulator for the beneficial agent, optionally associated with the beneficial agent; and

(g) an osmotic agent;

wherein at least the beneficial agent, optionally associated with the solubility modulator, is maintained separated from the solvent until the time of administration of the beneficial agent to a subject. In additional embodiments, the kit comprises a metering device, such as syringe, catheter, pump, syringe pump, autoinjector and the like.

Please replace paragraph number **[0034]** with the following rewritten paragraph:

[0034] ~~Figures~~ Figure 6C is a graph illustrating the *in vivo* release profile of human growth hormone obtained from various depot formulations, including those of the present invention (formulations 33, 35, 36, 39 and 40).

Please replace paragraph number **[0035]** with the following rewritten paragraph:

[0035] ~~Figures~~ Figure 6D ~~are graphs~~ is a graph illustrating the *in vivo* release profile of human growth hormone obtained from various depot formulations, including those of the present invention (formulations 34, 35, 37, 38 and 40).

Please replace paragraph number **[0048]** with the following rewritten paragraph:

[0048] Figure 19 is a graph illustrating the *in vivo* suppression of rat testosterone by the ~~3 month~~ 3-month leuprolide acetate depot formulations of the present invention (formulations 54 and 55) as compared with the placebo formulations without leuprolide acetate (formulations 56 and ~~56~~ 57).

Please replace paragraph number **[0051]** with the following rewritten paragraph:

Overview and Definitions:

[0051] The present invention is directed to an injectable depot composition for delivery of a beneficial agent to a subject over a prolonged duration of time, at multiple sites if required, and for multiple or repeated injections, ~~i.e.~~ i.e., for instances where the therapeutic effect of the beneficial agent has subsided or period of time for the beneficial agent to have a therapeutic effect has lapsed or for instances where the subject requires further administration of the beneficial agent for any reason, wherein the injectable depot composition serves as an implanted sustained release beneficial agent delivery system after injection into a patient's body. In particular, the invention provides controlled release of the beneficial agent to the subject being treated, the release being controlled over a period about, equal to or greater than two weeks and up to one year after administration, ~~i.e.~~ i.e., a period of about two weeks to about twelve months

after~~adminsitration,~~ administration, preferably over a period equal to or greater than one month after administration; more preferably over a period equal to or greater than 2 months after administration, preferably over a period equal to or greater than 3 months after administration, preferably over a period of about 3 months to about 9 months after administration, preferably over a period of about 3 months to about 6 months after administration, even more preferably over a period of up to about 3 months, up to about 4 months, up to about 5~~months;~~ months, and up to about 6 months after administration. The present invention also relates to a method of using the injectable depot composition to administer a beneficial agent to a patient.

Please replace paragraph number **[0052]** with the following rewritten paragraph:

[0052] The injectable depot composition is a gel formed from a polymer matrix comprising a bioerodible, biocompatible polymer; a solvent having a miscibility in water of less than or equal to 7 wt.% at 25° C, in an amount effective to plasticize the polymer and form a gel therewith; and a beneficial agent dissolved or dispersed in the gel. The present invention is also directed to a method of systemically or locally administering and delivering a beneficial agent to a subject ~~to include~~ by implanting in the subject an injectable depot composition as described above. The method of systemic or local delivery of the present invention is at multiple sites, if required, and is also directed toward multiple or repeated injections,~~i.e.~~ i.e., for instances where the therapeutic effect of the beneficial agent has subsided or period of time for the beneficial agent to have a therapeutic effect has lapsed or for instances where the subject requires further administration of the beneficial agent for any~~reason,~~ reason.

Please replace paragraph number **[0054]** with the following rewritten paragraph:

[0054] ~~It~~Surprisingly, it has been ~~surprisingly~~ found that the release rate of the beneficial agent from the injectable depot gel formulations of the invention can be varied by varying the polymer properties, such as the type of polymer, the molecular weight of the polymer (including the modal distribution of the polymer), and the comonomer ratio of the monomers forming the polymer, the end group of the polymers; the type of solvent; and by varying the

polymer/solvent ratios to provide a controlled, sustained release of a beneficial agent over a prolonged duration of time equal to or greater than two weeks and up to one year after administration, ~~i.e.~~ i.e., from about two weeks to about twelve months after administration, or preferably over a period from about one month to about twelve months after administration, preferably over a period equal to or greater than one month after ~~administration;~~ administration, more preferably over a period equal to or greater than 2 months after administration, preferably over a period equal to or greater than 3 months after administration, preferably over a period of about 3 months to about 9 months after administration, preferably over a period of about 3 months to about 6 months after administration, even more preferably over a period of up to about 3 months, up to about 4 months, up to about 5 ~~months;~~ months, and up to about 6 months after administration. The release rate profile and duration can be controlled by the appropriate choice of a polymer (including the ratio of the monomers, ~~e.g.~~ e.g., L/G, CL/L ratios), the molecular weight of the polymer (LMW, MMW, HMW), the end group of the polymer (acid, ester); a water immiscible solvent, the polymer/solvent ratio, emulsifying agent, pore former, solubility modifier for the beneficial agent, an osmotic agent, and the like.

Please replace paragraph number **[0058]** with the following rewritten paragraph:

[0058] Generally, the compositions of the invention are gel-like and form with a substantially homogeneous ~~non-~~nonporous structure throughout the implant upon implantation and during drug delivery, even as it hardens. Furthermore, while the polymer gel implant will slowly harden when subjected to an aqueous environment, the hardened implant may maintain a rubbery (~~non-~~nonrigid) composition with the glass transition temperature ~~Tg~~ T_g being below 37° C.

Please replace paragraph number **[0059]** with the following rewritten paragraph:

[0059] The preferred compositions herein allow beneficial agent to be loaded into the interior of the polymer at levels that are above that required to saturate the beneficial agent in water, thereby facilitating zero order release of beneficial agent. Additionally, the preferred

compositions may provide viscous gels that have a glass transition temperature that is less than 37° C, such that the gel remains ~~non-~~nonrigid for a period of time after implantation of 24 hours or more.

Please replace paragraph number **[0065]** with the following rewritten paragraph:

[0065] The term "burst index" means, with respect to a particular composition intended for systemic delivery of a beneficial agent, the quotient formed by dividing (i) the AUC calculated for the first time period after implantation of the composition into a subject divided by the number of hours in the first time period (t1), by (ii) the AUC calculated for the time period of delivery of beneficial agent, divided by the number of hours in the total duration of the delivery period (t2). For ~~example~~ example, the burst index at 24 hours is the quotient formed by dividing (i) the AUC calculated for the first twenty-four hours after implantation of the composition into a subject divided by the number 24, by (ii) the AUC calculated for the time period of delivery of beneficial agent, divided by the number of hours in the total duration of the delivery period.

Please replace paragraph number **[0069]** with the following rewritten paragraph:

[0069] The terms "prolonged period" or "prolonged duration" are used interchangeably and refer to a period of time over which release of a beneficial agent from the depot gel composition of the invention occurs, which will generally be over a period equal to or greater than two weeks or up to one year after administration, preferably over a period equal to or greater than one month after ~~administration;~~ administration, more preferably over a period equal to or greater than 2 months after administration, preferably over a period equal to or greater than 3 months after administration, preferably over a period of up to about 3 months to about 9 months after administration, preferably over a period of up to about 3 months to about 6 months after administration, and even more preferably over a period of up to about 3 months, up to about 4 months, up to about 5 months; and up to about 6 months after ~~administration~~ administration.

Please replace paragraph number **[0077]** with the following rewritten paragraph:

[0077] The term "low molecular weight (LMW) polymer" refers to bioerodible polymers having ~~a weight~~ an average molecular weight ranging from about ~~3000~~ 3,000 to about 10,000; preferably from about ~~3000~~ 3,000 to about 9,000; more preferably from about ~~4000~~ 4,000 to about 8,000; and more preferably the low molecular weight polymer has a molecular weight of about ~~7000~~ 7,000, about ~~6000~~ 6,000, about ~~5000~~ 5,000, about ~~4000~~ 4,000 and about ~~3000~~ 3,000 as determined by gel permeation chromatography (GPC).

Please replace paragraph number **[0078]** with the following rewritten paragraph:

[0078] The term "medium molecular weight (MMW) polymer" refers to biocompatible, bioerodible polymers having ~~a weight~~ an average molecular weight ranging from between about 10,000 to about 30,000; preferably from about 12,000 to about 20,000; more preferably from about 14,000 to about 18,000; and more preferably the medium molecular weight polymer has a molecular weight of about 14,000, about 15,000, about 16,000, about 17,000 and about 18,000 as determined by gel permeation chromatography (GPC). In preferred embodiments, a MMW polymer is selected from PLGA RG502, PLGA RG752, and PLA R202.

Please replace paragraph number **[0079]** with the following rewritten paragraph:

[0079] The term "high molecular weight (HMW) polymer" refers to biocompatible, bioerodible polymers having ~~a weight~~ an average molecular weight of greater than 30,000; preferably from about 30,000 to about 250,000; more preferably from about 30,000 to about 120,000 as determined by gel permeation chromatography (GPC). In preferred embodiments, a HMW polymer is selected from RG503, PLGA RG 755, PLA R206, PCL/PLA 75:25 and PCL/PLA 25:75.

Please replace paragraph number **[0082]** with the following rewritten paragraph:

[0082] The term "alkyl" as used herein refers to a saturated hydrocarbon group ~~typically~~ typically, although not ~~necessarily~~ necessarily, containing 1 to about 30 carbon atoms, such as

methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, octyl, decyl, and the like, as well as cycloalkyl groups such as cyclopentyl, cyclohexyl and the like. Generally, although again not necessarily, alkyl groups herein contain 1 to about 12 carbon atoms. The term "lower alkyl" intends an alkyl group of 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms. "Substituted alkyl" refers ~~to~~ to an alkyl substituted with one or more substituent groups, and the terms "heteroatom-containing alkyl" and "heteroalkyl" refer ~~to~~ to an alkyl in which at least one carbon atom is replaced with a heteroatom. If not otherwise indicated, the terms "alkyl" and "lower alkyl" include linear, branched, cyclic, unsubstituted, substituted, and/or heteroatom-containing alkyl or lower alkyl.

Please replace paragraph number **[0086]** with the following rewritten paragraph:

[0086] By "substituted" as in "substituted alkyl," "substituted aryl" and the like, as alluded to in some of the aforementioned definitions, is meant that in the alkyl or aryl moiety, respectively, at least one hydrogen atom bound to a carbon atom is replaced with one or more ~~non-~~noninterfering substituents such as hydroxyl, alkoxy, thio, amino, halo, and the like.

Please replace paragraph number **[0088]** with the following rewritten paragraph:

[0088] The polymer, solvent and other agents of the invention must be ~~biocompatible~~ biocompatible, that ~~is~~ is, they must not cause irritation or necrosis in the environment of use. The environment of use is a fluid environment and may comprise a subcutaneous, intramuscular, intravascular (high/low flow), intramyocardial, adventitial, intratumoral, or intracerebral portion, wound sites, tight joint spaces or body cavity of a human or animal. In certain embodiments, the beneficial agent may be administered locally to avoid or minimize systemic side effects. Gels of the present invention containing a beneficial agent may be injected/implanted directly into or applied as a coating to the desired location, e.g., subcutaneous, intramuscular, intravascular, intramyocardial, adventitial, intratumoral, or intracerebral portion, wound sites, tight joint spaces or body cavity of a human or animal.

Please replace paragraph number **[0089]** with the following rewritten paragraph:

[0089] Typically, the viscous gel will be injected from a standard hypodermic syringe through a needle, a catheter, or a trocar, that has been ~~pre-~~prefilled with the beneficial agent-viscous gel composition to form the depot. It is often preferred that injections take place using the smallest size needle (i.e., smallest diameter) to reduce discomfort to the subject when the injection is in a subcutaneous, intramuscular, intravascular (high/low flow), intramyocardial, adventitial, intratumoral, or intracerebral portion, wound sites, tight joint spaces or body cavity of a human or animal. It is desirable to be able to inject gels through a needle or a catheter ranging from 16 gauge and higher, preferably 20 gauge and higher, more preferably 22 gauge and higher, ~~even~~ and even more preferably 24 gauge and higher. With highly viscous gels, i.e., gels having a viscosity of about 200 poise or greater, injection forces to dispense the gel from a syringe having a needle in the 20-30 gauge range may be so high as to make the injection difficult or reasonably impossible when done manually. At the same time, the high viscosity of the gel is desirable to maintain the integrity of the depot after injection and during the dispensing period and ~~also~~ also to facilitate desired suspension characteristics of the beneficial agent in the gel.

Please replace paragraph number **[0090]** with the following rewritten paragraph:

A. The Bioerodible, Biocompatible Polymer:

[0090] Polymers that are useful in conjunction with the methods and compositions of the invention are bioerodible, i.e., they gradually ~~degrade~~ degrade, e.g., enzymatically or hydrolyze, dissolve, physically erode, or otherwise disintegrate within the aqueous fluids of a patient's body. Generally, the polymers bioerode as a result of hydrolysis or physical erosion, although the primary bioerosion process is typically hydrolysis or enzymatic degradation.

Please replace paragraph number **[0092]** with the following rewritten paragraph:

[0092] ~~It~~Surprisingly, it has been ~~surprisingly~~ found that the release rate of the beneficial agent from the injectable depot gel formulations of the invention can be varied by varying the polymer properties, such as the type of polymer, the molecular weight of the polymer

(including the modal distribution of the polymer), and the comonomer ratio of the monomers forming the polymer; the end group of the ~~polymers~~ polymers; the type of solvent; and by varying the polymer/solvent ratios to provide a controlled, sustained release of a beneficial agent over a prolonged duration of time equal to or greater than two weeks and up to one year after administration, preferably over a period equal to or greater than one month after administration; preferably over a period equal to or greater than 2 months after administration, preferably over a period equal to or greater than 3 months after administration, preferably over a period of about 3 months to about 9 months after administration, more preferably over a period of about 3 months to about 6 months after administration, preferably over a period of up to about 3 months, up to about 4 months, up to about 5 months; and up to about 6 months after administration. The release rate profile and duration can be controlled by the appropriate choice of a polymer (including the ratio of the monomers, ~~e.g.~~ e.g., L/G, CL/L ratios), the molecular weight of the polymer (LMW, MMW, HMW), the end group of the polymer (acid, ester); a water immiscible solvent, the polymer/solvent ratio, emulsifying agent, pore former, solubility modifier for the beneficial agent, an osmotic agent, and the like.

Please replace paragraph number **[0093]** with the following rewritten paragraph:

[0093] In another aspect, the present invention provides a method of regulating the release of a beneficial agent from an injectable depot composition. The duration and the rate of release of the beneficial agent (~~e.g.~~ e.g., burst index and release rate profile) are controlled by the appropriate choice of the biodegradable polymer, the molecular weight of the polymer, the comonomer ratio of the various monomers forming the polymer (e.g., the L/G or CL/L ratio for a lactic acid-based polymer), and the polymer/solvent ratios as tabulated in Tables A, B, C and D below. Previously described injectable depot formulations having polylactic acid (~~i.e.~~ i.e., a L/G ratio of 100:0) exhibit a release profile of the beneficial agent over a duration of about 3 months (which is shorter than the comparable depot composition of the instant invention, see e.g., Examples 20 and 21, and Figures 13, 16 and 17 as described in greater detail hereinafter). As illustrated in the Examples below, it has been discovered that PLGA depot gel compositions

of the invention having a L/G ratio of about 75:25 release the beneficial agent in a sustained manner over a period of approximately 3-4 months. In additional embodiments, PLGA depot gel compositions of the invention having a L/G ratio of about 100:0 (~~i.e.~~i.e., polylactic acid (PLA)) and a P/S ratio of about 55:45 to about 65:35, release the beneficial agent in a sustained manner over a period of approximately 6-8 months. In additional embodiments, PLGA depot gel compositions of the invention having a molecular weight of about 14,000 to about 22,000; a L/G ratio of about 75:25 to about 100:0 and a P/S ratio of about 50:50 to about 65:35, release the beneficial agent in a sustained manner over a period of approximately 3-8 months.

Please replace paragraph number **[0095]** with the following rewritten paragraph:

[0095] (A) Molecular weight of the polymer: The molecular weight~~of~~ of the polymer can be varied to regulate the release rate profile and/or delivery duration of the beneficial agent. In general, as the molecular weight of the polymer increases, one or more of the following occurs: the burst index is lower, release rate profile is flatter and/or duration of delivery is longer.

Please replace paragraph number **[0096]** with the following rewritten paragraph:

[0096] (B) Polymers with different end groups: Depot gel compositions having a blend of polymers with different end groups would result in a depot formulation having a lower burst index than those polymers that are not blended and a regulated duration of delivery. For example, blending PLGA RG502H (acid end group) with PLGA RG502 (ester end group) lowers the burst index for a depot gel composition having a one month duration of delivery; blending PLGA RG752H with PLGA RG752 lowers the burst index for a depot gel composition having a duration of delivery of about 3 months to about 4 months; blending PLA R202H with PLA R202 lowers the burst index for a depot gel composition~~having~~ having a duration of delivery greater than or equal to 6 months; blending PLGA RG502H and PLGA RG752 with PLA R202 lowers the burst index for a depot gel composition~~having~~ having a duration of delivery greater than or equal to 6 months. In accordance with the invention, the depot gel compositions comprise a

blend of polymers, ~~i.e.~~ i.e., a blend of polymer components, and preferably, the blend of polymers includes at least one lactic acid-based polymer as one of the polymer components of the depot gel composition.

Please replace paragraph number **[0098]** with the following rewritten paragraph:

[0098] (D) Polymers with different degradation characteristics: Depot gel compositions having a blend of a faster degrading polymer with a slower degrading polymer would result in a depot formulation having a lower burst index and a longer duration of delivery. For example, blending PLGA RG 502 with PLGA RG752 would yield a depot gel composition having a lower burst index (as compared to a gel composition having PLGA RG752 alone) ~~and~~ and a duration of delivery of about 3 months to about 4 months after administration. Blending PLGA RG502 and PLGA RG752 with PLA R202 would yield a depot gel composition having a lower burst index (as compared to a gel composition having PLA 202 alone) and a duration of delivery greater than or equal to 6 months after administration.

Please replace paragraph number **[0102]** with the following rewritten paragraph:

[0102] The bioerodible polymers are selected from the group consisting of low molecular weight (LMW) polymers, medium molecular weight (MMW) polymers and high molecular weight (HMW) polymers. The low molecular weight (LMW) bioerodible polymers have ~~weight~~ an average molecular weight ranging from about ~~3000~~ 3,000 to about 10,000; preferably from about ~~3000~~ 3,000 to about 9,000; more preferably from about ~~4000~~ 4,000 to about 8,000; and more preferably the low molecular weight polymer has a molecular weight of about ~~7000~~ 7,000, about ~~6000~~ 6,000, about ~~5000~~ 5,000, about ~~4000~~ 4,000 and about ~~3000~~ 3,000 as determined by gel permeation chromatography (GPC).

Please replace paragraph number **[0103]** with the following rewritten paragraph:

[0103] The medium molecular weight (MMW) bioerodible polymers have ~~weight~~ an average molecular weight ranging from between about 10,000 to about 30,000; preferably from

about 12,000 to about 20,000; more preferably from about 14,000 to about 18,000; and more preferably the medium molecular weight polymer has a molecular weight of about 14,000, about 15,000, about 16,000, about 17,000 and about 18,000 as determined by gel permeation chromatography (GPC). In preferred embodiments, ~~a~~ an MMW polymer is selected from PLGA RG502, PLGA RG752, and PLA R202.

Please replace paragraph number **[0104]** with the following rewritten paragraph:

[0104] The high molecular weight (HMW) bioerodible polymers have ~~weight~~ an average molecular weight of greater than 30,000; preferably from about 30,000 to about 250,000; more preferably from about 30,000 to about 120,000 as determined by gel permeation chromatography (GPC). In preferred embodiments, ~~a~~ an HMW polymer is selected from RG503, PLGA RG 755, PLA R206, PCL/PLA 75:25 and PCL/PLA 25:75.

Please replace paragraph number **[0105]** with the following rewritten paragraph:

[0105] Preferably, the polymer matrix comprises about 0 ~~wt %~~ wt.% to about 95 ~~wt%~~ wt.% of ~~low molecular weight (LMW)~~ LWM polymer, preferably about 20 ~~wt%~~ wt.% to about 90 ~~wt%~~ wt.% of ~~low molecular weight (LMW)~~ LMW polymer, more preferably about 30 ~~wt%~~ wt.% to about 80 ~~wt%~~ wt.% of ~~low molecular weight (LMW)~~ LMW polymer, and more preferably about 40 ~~wt%~~ wt.% to about 75 ~~wt%~~ wt.% of ~~low molecular weight (LMW)~~ LMW polymer; about 0 ~~wt%~~ wt.% to about 50 ~~wt%~~ wt.% of ~~high molecular weight (HMW)~~ HMW polymer, preferably about 5 ~~wt%~~ wt.% to about 40 ~~wt%~~ wt.% of ~~high molecular weight (HMW)~~ HMW polymer, more preferably about 10 ~~wt%~~ wt.% to about 30 ~~wt%~~ wt.% of ~~high molecular weight (HMW)~~ HMW polymer, and more preferably about 15 ~~wt%~~ wt.% to about 25 ~~wt%~~ wt.% of ~~high molecular weight (HMW)~~ HMW polymer; and about 0 ~~wt%~~ wt.% to about 95 ~~wt%~~ wt.% of ~~medium molecular weight (MMW)~~ MMW polymer, preferably about 20 ~~wt%~~ wt.% to about 90 ~~wt%~~ wt.% of ~~medium molecular weight (MMW)~~ MMW polymer, more preferably about 30 ~~wt%~~ wt.% to about 80 ~~wt%~~ wt.% of ~~medium molecular~~

~~weight (MMW)~~ MMW polymer, and more preferably about 40~~wt%~~ wt.% to about 65~~wt%~~ wt.% of~~medium molecular weight (MMW)~~ MMW polymer.

Please replace paragraph number **[0106]** with the following rewritten paragraph:

[0106] Presently preferred polymers are polylactides, that is, a lactic acid-based polymer that can be based solely on lactic acid or can be a copolymer based on lactic acid, glycolic acid and/or caprolactone-based polymers including caprolactone (CL), which may include small amounts of other comonomers that do not substantially affect the advantageous results, which can be achieved in accordance with the present invention. As used herein, the term "lactic acid" includes the isomers L-lactic acid, D-lactic acid, DL-lactic acid and lactide while the term "glycolic acid" includes glycolide. Most preferred are polymers selected from the group consisting of, polylactide polymers, commonly referred to as PLA, poly(lactide-co-glycolide)copolymers, commonly referred to as PLGA, and poly(caprolactone-co-lactic acid) (PCL-co-LA). The polymer may have a monomer ratio of lactic acid/glycolic acid (L/G) of from about 50:50 to about 100:0, preferably from about 60:40 to about 85:15, preferably from about 65:35 to about 75:25. In certain embodiments, when the desired duration of release of the beneficial agent is about one month, preferably the polymer has a L/G ratio of 50:50. In alternative embodiments, when the desired duration of release of the beneficial agent is about 2 months, preferably the polymer has~~a~~ an L/G ratio of 65:35; when the desired duration of release of the beneficial agent is about 3 months, preferably the polymer has~~a~~ an L/G ratio of 75:25; and when the desired duration of release of the beneficial agent is about 6 months, preferably the polymer has~~a~~ an L/G ratio ranging from about 85:15 to about 100:0.

Please replace paragraph number **[0108]** with the following rewritten paragraph:

[0108] As indicated in aforementioned U.S. Patent No. 5,242,910, the polymer can be prepared in accordance with the teachings of U.S. Patent No. 4,443,340. Alternatively, the lactic acid-based polymer can be prepared directly from lactic acid or a mixture of lactic acid and glycolic acid (with or without a further comonomer) in accordance with the techniques set forth

in U.S. Patent No. 5,310,865. The contents of all of these patents are incorporated by reference. Suitable lactic acid-based polymers are available commercially. The lactic acid-based polymer may be a ~~low molecular weight polymer (LMW)~~ LMW polymer; a ~~medium molecular weight polymer (MMW)~~ MMW polymer or a ~~high molecular weight (HMW)~~ HMW polymer or a combination thereof.

Please replace paragraph number **[0110]** with the following rewritten paragraph:

[0110] The biocompatible polymer is present in the gel composition in an amount ranging from about 5 to about 90% by weight, preferably from about 20 to about 80% by weight, preferably from about 30 to about 75% by weight, often about 35 to about 70% by weight of the viscous gel, and about 40 to about 65% by weight ~~the~~ of the viscous gel comprising the combined amounts of the biocompatible polymer and the solvent. The biodegradable, biocompatible lactic acid-based polymer is in an amount comprising about ~~5wt.%~~ 5 wt.% to about 90 wt.%, and preferably from about 25 wt.% to about 80 wt.%, and more preferably from about 35 wt.% to about 75 wt.%. The solvent will be added to polymer in amounts described below, to provide injectable depot gel compositions. .

Please replace paragraph number **[0112]** with the following rewritten paragraph:

[0112] The solvent must be biocompatible, should form a viscous gel with the polymer, and restrict water uptake into the implant. The solvent may be a single solvent or a mixture of solvents exhibiting the foregoing properties. The term ~~"solvent",~~ "solvent," unless specifically indicated otherwise, means a single solvent or a mixture of solvents. Suitable solvents will substantially restrict the uptake of water by the implant and may be characterized as immiscible in water, i.e., having a solubility in water of less than 7% by weight. Preferably, the solvents are five weight percent or less soluble in water; more preferably three weight percent or less soluble in water; and even more preferably one weight percent or less soluble in water. Most preferably the solubility of the solvent in water is equal to or less than 0.5 weight percent.

Please replace paragraph number **[0113]** with the following rewritten paragraph:

[0113] Water miscibility may be determined experimentally as follows: Water (1-5 g) is placed in a tared clear container at a controlled temperature, about 20° C, and weighed, and a candidate solvent is added dropwise. The solution is swirled to observe phase separation. When the saturation point appears to be reached, as determined by observation of phase separation, the solution is allowed to stand overnight and is ~~re-~~rechecked the following day. If the solution is still saturated, as determined by observation of phase separation, then the percent (w/w) of solvent added is determined. Otherwise more solvent is added and the ~~process~~ process is repeated. Solubility or miscibility is determined by dividing the total weight of solvent added by the final weight of the solvent/water mixture. When solvent mixtures are used, for example 20% triacetin and 80% benzyl benzoate, they are ~~pre-~~premixed prior to adding to the water.

Please replace paragraph number **[0117]** with the following rewritten paragraph:

[0117] In the ester of formula (II), R1 is substituted or unsubstituted aryl, aralkyl, heteroaryl or heteroaralkyl, preferably substituted or unsubstituted aryl or heteroaryl, more preferably monocyclic or bicyclic aryl or heteroaryl optionally substituted with one or more ~~non-~~noninterfering substituents such as hydroxyl, carboxyl, alkoxy, thio, amino, halo, and the like, still more preferably 5- or 6-membered aryl or heteroaryl such as phenyl, cyclopentadienyl, pyridinyl, pyrimadinyl, pyrazinyl, pyrrolyl, pyrazolyl, imidazolyl, furanyl, thiophenyl, thiazolyl, or isothiazolyl, and most preferably 5- or 6-membered aryl. R2 is hydrocarbyl or heteroatom-substituted hydrocarbyl, typically lower alkyl or substituted or unsubstituted aryl, aralkyl, heteroaryl or heteroaralkyl, preferably lower alkyl or substituted or unsubstituted aralkyl or heteroaralkyl, more preferably lower alkyl or monocyclic or bicyclic aralkyl or heteroaralkyl optionally substituted with one or more ~~non-~~noninterfering substituents such as hydroxyl, carboxyl, alkoxy, thio, amino, halo, and the like, still more preferably lower alkyl or 5- or 6-membered aralkyl or heteroaralkyl, and most preferably lower alkyl or 5- or 6-membered aryl optionally substituted with one or more additional ester groups having the structure -O-(CO)-Rl. Most preferred esters are benzoic acid and phthalic acid derivatives.

Please replace paragraph number [0120] with the following rewritten paragraph:

[0120] Art recognized phthalic acid derivatives from which solvents having the requisite solubility may be selected include: Alkyl benzyl phthalate, bis-cumyl-phenyl isophthalate, dibutoxyethyl phthalate, dimethyl phthalate, dimethyl phthalate, diethyl phthalate, dibutyl phthalate, diisobutyl phthalate, butyl octyl phthalate, diisoheptyl phthalate, butyl octyl phthalate, diisononyl phthalate, nonyl undecyl phthalate, dioctyl phthalate, di-isooctyl phthalate, dicapryl phthalate, mixed alcohol phthalate, di-(2-ethylhexyl) phthalate, linear~~heptyl, nonyl,~~ heptyl nonyl phthalate, linear~~heptyl, nonyl,~~ heptyl nonyl undecyl phthalate, linear nonyl phthalate, linear nonyl undecyl phthalate, linear dinonyl, didecyl phthalate (diisodecyl phthalate), diundecyl phthalate, ditridecyl phthalate, undecyldodecyl phthalate, decyltridecyl phthalate, blend (50/50) of dioctyl and didecyl phthalates, butyl benzyl phthalate, and dicyclohexyl phthalate.

Please replace paragraph number [0122] with the following rewritten paragraph:

[0122] Preferred solvents include aromatic alcohols, the lower alkyl and aralkyl esters of the aryl acids described above. Representative acids are benzoic acid and the phthalic acids, such as phthalic acid, isophthalic acid, and~~terephathalic~~ terephthalic acid. Most preferred solvents are benzyl alcohol and derivatives of benzoic acid and include, but are not limited to, methyl benzoate, ethyl benzoate, n-propyl benzoate, isopropyl benzoate, butyl benzoate, isobutyl benzoate, sec-butyl benzoate, tert-butyl benzoate, isoamyl benzoate and benzyl benzoate, with benzyl benzoate being most especially preferred.

Please replace paragraph number [0123] with the following rewritten paragraph:

[0123] The composition may also include, in addition to the water-immiscible solvent(s), one or more additional miscible solvents ("component solvents"), provided that any such additional solvent is other than a lower alkanol. Component solvents compatible and miscible with the primary solvent(s) may have a higher miscibility with water and the resulting mixtures may still exhibit significant restriction of water uptake into the implant. Such mixtures

will be referred to as "component solvent mixtures." Useful component solvent mixtures may exhibit solubilities in water greater than the primary solvents themselves, typically between 0.1 weight percent and up to and including 50 weight percent, preferably up to and including 30 weight percent, and most preferably up to ~~an~~ and including 10 weight percent, without detrimentally affecting the restriction of water uptake exhibited by the implants of the invention.

Please replace paragraph number **[0124]** with the following rewritten paragraph:

[0124] Component solvents useful in component solvent mixtures are those solvents that are miscible with the primary solvent or solvent mixture, and include, but are not limited, to triacetin, diacetin, tributyrin, triethyl citrate, tributyl citrate, acetyl triethyl citrate, acetyl tributyl citrate, triethylglycerides, triethyl phosphate, diethyl phthalate, diethyl tartrate, mineral oil, polybutene, silicone fluid, ~~glylcerin,~~ glycerin, ethylene glycol, polyethylene glycol, octanol, ethyl lactate, propylene glycol, propylene carbonate, ethylene carbonate, butyrolactone, ethylene oxide, propylene oxide, N-methyl-2-pyrrolidone, 2-pyrrolidone, glycerol formal, glycofurol, methyl acetate, ethyl acetate, methyl ethyl ketone, dimethylformamide, dimethyl sulfoxide, tetrahydrofuran, caprolactam, decylmethylsulfoxide, oleic acid, and ~~1~~ 1-dodecylazacyclo-heptan-2-one, and mixtures thereof.

Please replace paragraph number **[0127]** with the following rewritten paragraph:

[0127] In an especially preferred embodiment, the primary solvent is selected from an aromatic alcohol and lower alkyl and aralkyl esters of benzoic acid and the polymer is a lactic-acid based polymer, most preferably selected from polylactide polymers (PLA), poly(lactide-co-glycolide) copolymers (PLGA), and poly(caprolactone-co-lactic acid) (PCL-co-LA) having a comonomer L/G ratio of about 50:50 to about 100:0 and an L/CL ratio of about 25:75 to about 75:25; and a polymer solvent ratio of about 40:60 to about 65:35. Preferably the polymer has ~~a weight~~ an average molecular weight ranging from about 3,000 to about 120,000; preferably from about 7,000 to about 100,000; more preferably from about 10,000 to about 80,000; and more preferably the polymer has a molecular weight of

about 14,000, about 16,000, about 20,000, about 30,000 and about 60,000. Presently, the most preferred solvents are benzyl alcohol, benzyl benzoate and the lower alkyl esters of benzoic acid, ~~e.g.~~ e.g., ethyl benzoate. The primary solvents, e.g., aromatic alcohol and benzoic acid ~~esters~~ esters, may be used alone or in a mixture with other miscible solvents, e.g., triacetin, or thixotropic agents, ~~e.g.~~ e.g., ethanol, as described herein.

Please replace paragraph number [0128] with the following rewritten paragraph:

[0128] The solvent or solvent mixture is capable of dissolving the polymer to form a viscous gel that can maintain particles of the beneficial agent dissolved or dispersed and isolated from the environment of use prior to release. The compositions of the present invention provide implants useful both for systemic and local administration of beneficial agent, the implants having a low burst index. Water uptake is controlled by the use of a solvent or component solvent mixture that ~~solublizes~~ solubilizes or plasticizes the polymer but substantially restricts uptake of water into implant. Additionally, the preferred compositions may provide viscous gels that have a glass transition temperature that is less than 37° C, such that the gel remains ~~non-~~ nonrigid for a period of time after implantation of 24 hours or more.

Please replace paragraph number [0130] with the following rewritten paragraph:

[0130] In addition to the control of water uptake and associated initial burst by choice of solvent, agents that modulate the water solubility of the beneficial agent can also be utilized in conjunction with the preferred solvents to control burst of beneficial agent from the implant. Burst indices and percent of beneficial agent released in the first twenty-four hours after implantation may be reduced by one-third to two-thirds or more by the use of solubility modulators associated with the beneficial agent. Such modulators are typically coatings, substances that form complexes or otherwise associate with or stabilize the beneficial agent such as metallic ions, other stabilizing agents, waxes, lipids, oils, ~~non-~~nonpolar emulsions, and the like. Use of such solubility modulators may permit the use of more highly water soluble solvents or mixtures and achieve burst indices of 8 or less for systemic applications, or with respect to

local applications. Typically, the implant systems useful in this invention will release, in the first 2 days after implantation, 60% or less of the total amount of beneficial agent to be delivered to the subject from the implant system, preferably 50% or less, more preferably 40% or less and even more preferably 30% or less.

Please replace paragraph number **[0133]** with the following rewritten paragraph:

[0133] Limited water uptake by the solvent-polymer compositions of the present invention results in the implant compositions being formed without the finger-like pores in the surface of implants formed using prior art processes. Typically, a composition of the present invention takes the form of a ~~substantially,~~ substantially homogeneous, sponge-like gel, with the pores in the interior of the implant being much the same as the pores on the surface of the implant. Compositions of the present invention retain their gel-like consistency and administer a beneficial agent in a controlled manner, at a sustained rate over a short duration of time than do prior art devices. This is possible with the appropriate choice of polymers and water immiscible solvents, and further since the injectable depot gel compositions of the present invention generally have a glass transition temperature, ~~Tg,~~ T_g, of less ~~than~~ than the body temperature of the subject, ~~e.g.~~ e.g., 37° C for humans. Because of the immiscibility of the solvents that are useful in this invention with water, water uptake by the implant is restricted and the pores that do form tend to resemble a closed cell structure without significant numbers of larger pores or pores extending from the surface into the interior of the implant being open at the surface of the implant. Furthermore, the surface pores offer only a limited opportunity for water from body fluids to enter the implant immediately after implantation, thus controlling the burst effect. Since the compositions often will be highly viscous prior to implantation, when the composition is intended for implantation by injection, the viscosity optionally may be modified by the use of viscosity-reducing, miscible solvents ~~or~~ or by the use of emulsifiers, or by heating to obtain a gel composition having a viscosity or shear resistance low enough to permit passage of the gel composition through a needle.

Please replace paragraph number **[0135]** with the following rewritten paragraph:

[0135] Depending on the particular solvent or solvent mixture selected, the polymer and beneficial agent, and optionally solubility modulators of the beneficial agent, the compositions of the present invention intended for systemic delivery may provide a gel composition having a burst index of 8 or less, preferably 6 or less, more preferably 4 or less and most preferably 2 or less. Compositions of PLGA ~~weight~~ with an average molecular weight ranging from about 3,000 to about 120,000 are desired; preferably from about 7,000 to about 100,000; more preferably from about 10,000 to about 80,000; and more preferably the polymer has a molecular weight of about 14,000 to about 60,000, with solvents having a miscibility in water of less than 7% by weight, optionally combined with the other solvents, providing implants intended for systemic delivery of beneficial agent having a burst index of 10 or less, preferably 7 or less, more preferably 5 or less and most preferably 3 or less, are particularly advantageous. The use of solvent mixtures as discussed herein can be particularly advantageous as a means of providing sufficient plasticizing of the polymer to obtain viscous gel formation and at the same time meet the desired burst indices and percentage release objectives of the compositions of the invention.

Please replace paragraph number **[0136]** with the following rewritten paragraph:

[0136] Compositions intended for local delivery of beneficial agent are formed in the same manner as those intended for systemic use. However, because local delivery of beneficial agent to a subject will not result in detectable plasma levels of beneficial agent, such systems have to be characterized by percentage of beneficial agent released in a predetermined initial period, rather than a burst index as defined herein. Most typically, that period will be the first 24 hours after implantation and the percentage will be equal to the amount by weight of the beneficial agent released in the period (~~e.g.~~ e.g., 24 hours) divided by the amount by weight of the beneficial agent intended to be delivered in the duration of the delivery period; multiplied by the number 100. Compositions of the present invention will have initial bursts of 40% or less, preferably 30% or less, most preferably 20% or less, for most applications.

Please replace paragraph number **[0137]** with the following rewritten paragraph:

[0137] In many instances, it may be desirable to reduce the initial burst of beneficial agent during local administration to prevent adverse effects. For example, implants of the invention containing chemotherapeutic agents are suitable for direct injection into tumors. However, many chemotherapeutic agents may exhibit toxic side effects when administered systemically. Consequently, local administration into the tumor may be the treatment method of choice. It is necessary, however, to avoid administration of a large burst of the chemotherapeutic agent if it is possible that such agent would enter the vascular or lymphatic systems where it may exhibit side affects. Accordingly, in such ~~instances~~ instances, the implantable systems of the present invention having limited burst as described herein are advantageous.

Please replace paragraph number **[0138]** with the following rewritten paragraph:

[0138] The gel formed by mixing the polymer and the solvent typically exhibits a viscosity of from about 100 to about 50,000 poise, preferably from about 500 to about 30,000 poise, more preferably from about 500 to about 10,000 poise measured at a 1.0 ~~sec-1~~ sec^{-1} shear rate and 25° C using a Haake Rheometer at about 1-2 days after mixing is completed. Mixing the polymer with the solvent can be achieved with conventional low shear equipment such as a Ross double planetary mixer for from about 10 minutes to about 1 hour, although shorter and longer periods may be chosen by one skilled in the art depending on the particular physical characteristics of the composition being prepared. Since the depot gel composition of the invention ~~are~~ is administered as an injectable composition, a countervailing consideration when forming depot gel compositions that are viscous gels is that the polymer/solvent/ beneficial agent composition have sufficiently low viscosity in order to permit it to be forced through a small diameter, e.g., 18-20 gauge needle. If necessary, adjustment of viscosity of the gel for injection can be accomplished with emulsifying agents as described herein. Yet, such compositions should have adequate dimensional stability so as to remain localized and be able to be removed if necessary. The particular gel or gel-like compositions of the present invention satisfy such requirements.

Please replace paragraph number [0141] with the following rewritten paragraph:

[0141] When used, the emulsifying agent typically is present in an amount ranging from about 5 to about 80%, preferably from about 20 to about 60% and often 30 to 50% by weight based on the amount of the injectable depot gel ~~composition,~~ composition that is the combined amounts of polymer, solvent, emulsifying agent and beneficial agent. Emulsifying agents include, for example, solvents that are not fully miscible with the polymer solvent or solvent mixture. Illustrative emulsifying agents are water, alcohols, polyols, esters, carboxylic acids, ketones, aldehydes and mixtures thereof. Preferred emulsifying agents are alcohols, propylene glycol, ethylene glycol, glycerol, water, and solutions and mixtures thereof. Especially preferred are water, ethanol, and isopropyl alcohol and solutions and mixtures thereof. The type of emulsifying agent affects the size of the dispersed droplets. For instance, ethanol will provide droplets that have average diameters that can be on the order of ten times larger than the droplets obtained with an isotonic saline solution containing 0.9% by weight of sodium chloride at 21° C.

Please replace paragraph number [0143] with the following rewritten paragraph:

[0143] Although the injectable depot gel composition of the present invention preferably ~~are~~ is formed as viscous gels, the means of administration of the implants is not limited to injection, although that mode of delivery may often be preferred. Where the injectable depot gel composition will be administered as a leave-behind product, it may be formed to fit into a body cavity existing after completion of surgery or it may be applied as a flowable gel by brushing or palleting the gel onto residual tissue or bone. Such applications may permit loading of beneficial agent in the gel above concentrations typically present with injectable compositions.

Please replace paragraph number [0146] with the following rewritten paragraph:

[0146] Examples of drugs which may be delivered by the composition of the present invention include, but are not limited to ~~bupivicaine,~~ bupivacaine, buprenorphine, prochlorperzine edisylate, ferrous sulfate, aminocaproic acid, mecamylamine hydrochloride, procainamide hydrochloride, amphetamine sulfate, methamphetamine hydrochloride,

benzamphetamine hydrochloride, isoproterenol sulfate, phenmetrazine hydrochloride, bethanechol chloride, methacholine chloride, pilocarpine hydrochloride, atropine sulfate, scopolamine bromide, isopropamide iodide, tridihexethyl chloride, phenformin hydrochloride, methylphenidate hydrochloride, theophylline cholinate, cephalexin hydrochloride, diphenidol, meclizine hydrochloride, prochlorperazine maleate, phenoxybenzamine, thiethylperzine maleate, anisindone, diphenadione erythrityl tetranitrate, digoxin, isoflurophate, acetazolamide, methazolamide, bendroflumethiazide, chloropromaide, tolazamide, chlormadinone acetate, phenaglycodol, allopurinol, aluminum aspirin, methotrexate, acetyl sulfisoxazole, erythromycin, hydrocortisone, hydrocorticosterone acetate, cortisone acetate, dexamethasone and its derivatives such as betamethasone, triamcinolone, methyltestosterone, testosterone, 17-S-estradiol, ethinyl estradiol, ethinyl estradiol 3-methyl ether, prednisolone, 17α-hydroxyprogesterone acetate, 19-nor-progesterone, norgestrel, norethindrone, norethisterone, norethiederone, progesterone, norgesterone, norethynodrel, aspirin, indomethacin, naproxen, fenoprofen, sulindac, indoprofen, nitroglycerin, isosorbide dinitrate, propranolol, timolol, atenolol, alprenolol, cimetidine, clonidine, imipramine, levodopa, chlorpromazine, methyldopa, dihydroxyphenylalanine, theophylline, calcium gluconate, ketoprofen, ibuprofen, cephalexin, erythromycin, haloperidol, zomepirac, ferrous lactate, vincamine, diazepam, phenoxybenzamine, diltiazem, milrinone, mandol, quanbenz, hydrochlorothiazide, ranitidine, flurbiprofen, fenufen, fluprofen, tolmetin, alclofenac, mefenamic, flufenamic, difuinal, nimodipine, nitrendipine, nisoldipine, nicardipine, felodipine, lidoflazine, tiapamil, gallopamil, amlodipine, mioflazine, lisinolpril, enalapril, enalaprilat, captopril, ramipril, famotidine, nizatidine, sucralfate, etintidine, tetratolol, minoxidil, chlordiazepoxide, diazepam, amitriptyline, imipramine, paliperidone, resperidone, octreotide, alendronate, α-4,β^{-7} receptor antagonist ~~leukosite~~ leukocyte and infliximab (Remicade). Further examples are proteins and peptides which include, but are not limited to, bone morphogenic proteins, insulin, colchicine, glucagon, thyroid stimulating hormone, parathyroid and pituitary hormones, calcitonin, renin, prolactin, corticotrophin, thyrotropic hormone, follicle stimulating hormone, chorionic gonadotropin, gonadotropin releasing hormone, bovine somatotropin, porcine somatotropin, oxytocin, vasopressin, GRF, somatostatin, lypressin, pancreozymin,

luteinizing hormone, LHRH, LHRH agonists and antagonists, leuprolide, interferons such as interferon alpha-2a, interferon alpha-2b, and consensus interferon, interleukins, growth hormones such as human growth hormone and its derivatives such as methione-human growth hormone and des-phenylalanine human growth hormone, parathyroid hormone, bovine growth hormone and porcine growth hormone, fertility inhibitors such as the prostaglandins, fertility promoters, growth factors such as epidermal growth factors (EGF), platelet-derived growth factors (PDGF), fibro-blast growth factors (FGF), transforming growth factors-α (TGF-α), transforming growth factors-β (TGF-β), erythropoietin (EPO), insulin-like growth factor-I-(IGF-I), insulin-like growth factor-II (IGF-II), interleukin-1, interleukin-2, interleukin-6, interleukin-8, tumor necrosis factor-α (TNF-α), tumor necrosis factor-β (TNF-β), Interferon-α (INF-α), Interferon-β (INF-β), Interferon-γ (INF-γ), Interferon-ω (INF-ω), colony stimulating factors (CGF), vascular cell growth factor (VEGF), thrombopoietin (TPO), stromal cell-derived factors (SDF), placenta growth factor (PIGF), hepatocyte growth factor (HGF), granulocyte macrophage colony stimulating factor (GM-CSF), glial-derived neurotropin factor (GDNF), granulocyte colony stimulating factor (G-CSF), ciliary neurotropic factor (CNTF), bone growth factor, transforming growth factor, bone morphogeneic proteins (BMP), coagulation factors, human pancreas hormone releasing factor, analogs and derivatives of these compounds, and pharmaceutically acceptable salts of these compounds, or their analogs or derivatives.

Please replace paragraph number **[0147]** with the following rewritten paragraph:

[0147] The present invention also finds application with chemotherapeutic agents for the local application of such agents to avoid or minimize systemic side effects. Gels of the present invention containing chemotherapeutic agents may be injected directly into the tumor tissue for sustained delivery of the chemotherapeutic agent over time. In some cases, particularly after resection of the tumor, the gel may be implanted directly into the resulting cavity or may be applied to the remaining tissue as a coating. In cases in which the gel is implanted after surgery, it is possible to utilize gels having higher viscosities since they do not have to pass through a small diameter needle. Representative chemotherapeutic agents that may be delivered in

accordance with the practice of the present invention include, for example, carboplatin, cisplatin, paclitaxel, 5-fluorouracil, BCNU, vincristine, camptothecin, etopside, cytokines, ribozymes, interferons, oligonucleotides and oligonucleotide sequences that inhibit translation or transcription of tumor genes, functional derivatives of the foregoing, and generally known chemotherapeutic agents such as those described in U.S. Patent 5,651,986. The present application has particular utility in the sustained delivery of water soluble chemotherapeutic agents, such ~~as~~ as, for ~~example~~ example, cisplatin and carboplatin and the water soluble derivatives of paclitaxel. Those characteristics of the invention that minimize the burst effect are particularly advantageous in the administration of water soluble beneficial agents of all kinds, but particularly those compounds that are clinically useful and effective but may have adverse side effects.

Please replace paragraph number **[0154]** with the following rewritten paragraph:

[0154] Release rates and loading of beneficial agent will be adjusted to provide for therapeutically-effective delivery of the beneficial agent over the intended sustained delivery period. Preferably, the beneficial agent will be present in the polymer gel at concentrations that are above the saturation concentration of beneficial agent in water to provide a drug reservoir from which the beneficial agent is dispensed. While the release rate of beneficial agent depends on the particular circumstances, such as the beneficial agent to be administered, release rates on the order of from about 0.1 to about ~~10000~~ 10,000 micrograms/day, preferably from about 1 to about ~~5000~~ 5,000 micrograms per day, for periods of from about 2 weeks to about one year can be obtained. Greater amounts may be delivered if delivery is to occur over shorter periods. Generally, ~~higher~~ a higher release rate is possible if a greater burst can be tolerated. In instances where the gel composition is surgically implanted, or used as a "leave behind" depot when surgery to treat the disease state or another condition is concurrently conducted, it is possible to provide higher doses ~~that~~ than would normally be administered if the implant was injected. Further, the dose of beneficial agent may be controlled by adjusting the volume of the gel implanted or the injectable gel injected.

Please replace paragraph number **[0155]** with the following rewritten paragraph:

[0155] Figures ~~6 A-D~~ 6A-D and 7-21 illustrate representative release profiles of various beneficial agents obtained in rats from preferred compositions of this invention. As illustrated in the figures, the injectable depot gel formulations of the invention comprising polymers provide a controlled, sustained release of a beneficial agent over a specified/desired duration of time. The duration and the release rate profiles can be adjusted depending on the nature of the polymer and the properties of the polymer (~~e.g.~~ e.g., MW, comonomer ratios, end-group)~~; the~~, and the nature of the solvent and the polymer/solvent ratio.

Please replace paragraph number **[0157]** with the following rewritten paragraph:

[0157] The thixotropic agent,~~i.e.~~ i.e., an agent that imparts thixotropic properties to the polymer gel, is selected from the lower alkanols. Lower alkanol means an alcohol that contains 2-6 carbon atoms and is straight chain or branched chain. Such alcohols may be exemplified by ethanol, isopropanol, and the like. Importantly, such a thixotropic agent is not a polymer solvent. (~~See~~See, e.g., *Development of an in situ forming ~~bidegradable~~ biodegradable poly-lactide-co-glycolide system for controlled release of proteins,* Lambert, W.J., and Peck, K.D., *Journal of Controlled Release,* 33 (1995) 189-195).

Please replace paragraph number **[0158]** with the following rewritten paragraph:

[0158] Pore forming agents ~~include,~~ include biocompatible materials that when contacted with body fluids dissolve, disperse or degrade to create pores or channels in the polymer matrix. Typically, organic and ~~non-~~nonorganic materials that are water soluble such as sugars (e.g., sucrose, dextrose), water soluble salts (e.g., sodium chloride, sodium phosphate, potassium chloride, and sodium carbonate), water soluble solvents such as N-methyl-2-pyrrolidone and polyethylene glycol and water soluble polymers (e.g., carboxmethylcellulose, hydroxypropylcellulose, and the like) can conveniently be used as pore formers. Such materials may be present in amounts varying from about 0.1% to about 100% of

the weight of the polymer, but will typically be less than 50% and more typically less than 10-20% of the weight of polymer.

Please replace paragraph number [0162] with the following rewritten paragraph:

Example 1

Depot Vehicle Preparation

[0162] A gel vehicle for use in an injectable depot of the composition was prepared as follows. A glass vessel was tared on a Mettler AE 163 analytical balance or a Mettler PJ3000 top loader balance. Poly (D,L-lactide-co-glycolide) (PLGA), (L/G ratio of 50/50) with an inherent viscosity of 0.15 (PLGA-BPI, Birmingham Polymers, Inc., Birmingham, AL); Resomer® PLGA RG502 (L/G ratio of 50/50), Resomer® PLGA RG503 (L/G ratio of 50/50); 50:50 Resomer® RG504 (PLGARG 504); or a Poly (D,L-lactide-co-glycolide) (PLGA) (L/G ratio of 75/25, Resomer® RG752 (Boehringer Ingeheim Chemicals Inc., Petersburg, VA), were milled and sieved below 425~~micron~~ microns. The polymer was weighed into the glass vessel. The glass vessel containing the polymer was tared and the corresponding solvent was added. Amounts expressed as percentages for various polymer/solvent combinations are set forth in Table 1, below. The polymer/solvent mixture was stirred at 250 ± 50 rpm (IKA electric stirrer, IKH-Werke GmbH and Co., Stanfen, Germany) for about 5 - 10 minutes, resulting in a sticky paste-like substance containing polymer particles. The vessel containing the polymer/solvent mixture was sealed and placed in a temperature-controlled incubator equilibrated to 37° C for 1 to 4 days, with intermittent stirring, depending ~~on~~ on the type and/or amount of solvent and polymer. The polymer/solvent mixture was removed from the incubator when it appeared to be a clear amber homogeneous solution. Thereafter, the mixture was placed in an oven (65° C, 30 minutes) until polymer was dissolved in the mixture.

Please replace paragraph number [0164] with the following rewritten paragraph:

[0001] [0164] Lyophilized particles were prepared from tris buffer solutions (5 or 50 mM: pH 7.6) containing hGH (5 mg/mL) using a Durastop µP Lyophilizer in accordance with the following freezing and drying cycles:

Freezing cycle	Ramp down at ~~2.5~~ 2.5° C~~C~~/min to -30° C to and hold for 30 min
	Ramp down at ~~2.5 C~~ 2.5° C/min to -30° C and hold for 30 min
Drying cycle	Ramp up at ~~0.5 C~~ 0.5° C/min to 10° C and hold for 960 min
	Ramp up at ~~0.5 C~~ 0.5° C/min to 20° C and hold for 480 min
	Ramp up at ~~0.5 C~~ 0.5° C/min to 25° C and hold for 300 min
	Ramp up at ~~0.5 C~~ 0.5° C/min to 30° C and hold for 300 min
	Ramp up at ~~0.5 C~~ 0.5° C/min to 5° C and hold for ~~5000~~ 5,000 min

Please replace paragraph number [0165] with the following rewritten paragraph:

Example 3

~~HGH~~hGH-Stearic Acid Particle Preparation

[0165] Human growth hormone (hGH) particles were prepared as follows: Lyophilized hGH (3.22 grams, Pharmacia-Upjohn, Stockholm, Sweden) and stearic acid (3.22 grams, 95% pure, Sigma-Aldrich Corporation, St. Louis, MO) were blended and ground. The ground material was compressed in a 13 mm round die, with a force of 10,000 pounds for 5 minutes. Compressed tablets were ground and sieved through a 70 mesh screen followed by a 400 mesh screen to obtain particles having a size range between 38 - 212 microns.

Please replace paragraph number **[0166]** with the following rewritten paragraph:

Example 4

Bupivacaine base Preparation

[0166] Bupivacaine hydrochloride (Sigma-Aldrich Corporation, St. Louis, MO) was dissolved in ~~de-~~deionized (DI) water at a concentration of 40 mg/ml (saturation). A calculated amount of sodium hydroxide (in the form of 1 N solution) was added to the solution and the pH of the final mixtures was adjusted to 10 to precipitate the Bupivacaine base. The precipitated product was filtered, and further washed with DI water ~~for at~~ at least three times. The precipitated product was dried at ca. 40° C in vacuum for 24 ~~h~~ hours.

Please replace paragraph number **[0167]** with the following rewritten paragraph:

Example 5

Bupivacaine Particle Preparation

[0167] Bupivacaine drug particles (both base and hydrochloride salt) were prepared as follows. Bupivacaine hydrochloride (Sigma-Aldrich Corporation, St. Louis, MO) or bupivacaine base prepared ~~according~~ according to Example 4 were grounded and then sieved to a fixed range using 3" stainless steel sieves. Typical ranges include 25μm to 38μm, 38μm to 63μm, and 63μm to 125μm.

Please replace paragraph number **[0169]** with the following rewritten paragraph:

Example 7

Preparation of Leuprolide Acetate Particles

[0169] Leuprolide acetate (Mallinckrodt Inc., St. Louis, ~~MI~~ MO) was ground and sieved between ~~63-125 μm~~ 63-125μm sieves (for nominal particle size of ~~90 μm~~ 90μm). An GILSON digital Sieve Shaker may be employed to speed the sieving (Gilson Company Inc., Worthington, OH).

Please replace paragraph number **[0170]** with the following rewritten paragraph:

Example 8

Preparation of Leuprolide Acetate-Stearic Acid Particles

[0170] Stearic acid (95% pure, Sigma-Aldrich Corporation, St. Louis, MO) was passed through a 120-mesh screen (~~125 µm~~125µm). Equal amounts of milled leuprolide acetate (~~<63 µm~~<63µm, prepared as described in Example 2 above) and sieved stearic acid were transferred to the Waring blender and blended for 30 seconds. The blended materials were compressed in a 13 mm round die ~~using~~ using a compression force of ~~5000~~ 5,000 lbs and hold time of 5 min. Compressed pellets were ground and sieved through a 120-mesh (~~125 µm~~125µm) sieve and retained on a 230 mesh (~~63 µm~~63µm) sieve.

Please replace paragraph number **[0171]** with the following rewritten paragraph:

Example 9

Preparation of Buprenorphine Particles

[0171] Buprenorphine hydrochloride (100 grams, Sigma-Aldrich Corporation, St. Louis, MO) was ground and sieved through ~~pre-~~preselected sieves such as 25, 38, 62 or 125 micron sieves depending on the desirable particle sizes to obtain the corresponding Buprenorphine particles.

Please replace paragraph number **[0172]** with the following rewritten paragraph:

Example 10

Preparation of Buprenorphine-Stearic Acid Particles

[0172] Equal ~~amount~~ amounts of Buprenorphine particles (prepared as described in Example 4~~) above~~ above) and stearic acid (prepared as described in Example 3) were blended and ground. The ground material was compressed in a 13 mm round die, with a force of 5,000 pounds for 5 minutes. Compressed tablets were ground and sieved through a 120 mesh screen followed by a 230 mesh screen to obtain particles having a size range between 63-125 microns.

Please replace paragraph number **[0174]** with the following rewritten paragraph:

[0174]

Table 4

Formulation	PLGA RG502[4a] (wt%)	LMW PLGA (wt%)	Benzyl Benzoate (wt%)
17[4c]	45	0[4b]	45
18[4c]	0	45[4b]	45
19[4d]	45	0[4b]	45
20[4d]	0	45[4b]	45
21[4f]	45	0[4e]	45
22[4f]	0	45[4e]	45
23[4f]	0	63[4e]	27

4a = PLGA RG 502, MW = 16,000.
4b = Low Molecular Weight (LMW, MW = ~~8000~~ 8,000) PLGA with an ester end group.
4c = 10% bupivacaine hydrochloride loading.
4d = 10% bupivacaine base loading.
4e = Low Molecular Weight (LMW, MW - 7,000) PLGA with an ester end group
4f = 5% hGH loading.

Table 5

Formulation	LMW PLGA[5g] (wt%)	LMW PLGAc[5h] (wt%)	Benzyl Benzoate (wt%)	Benzyl Alcohol (wt%)
24[5i]	58.5	0	31.5	0
25[5i]	58.5	0	0	31.5
26[5i]	67.5	0	0	22.5
27[5i]	0	67.5		22.5
28[5j]	0	60		20

5g = Low Molecular Weight (LMW, MW = 8,000) PLGA with an ester end group.
5h = Low Molecular Weight (LMW, MW = 10,000) PLGA with a carboxyl end group.
5i = 10% bupivacaine hydrochloride loading.
5j = 10% bupivacaine hydrochloride and 10% SA loading.

Table 6

Formulation	Polymer[6a] (%)	Benzyl Benzoate (%)	Ethanol (%)
29[6b]	45.0	45.0	0.0
30[6c]	40.0	40.0	0.0
31[6c]	45.0	44.0	1.0
32[6c]	39.0	39.0	2.7
33[6b]	39.0	39.7	0.0
34[6c]	31.9	47.6	0.3
35[6c]	33.5	44.0	0.3
36[6c]	40.2	36.0	0.9
37[6c]	32.4	44.2	1.2
38[6c]	32.3	44.0	1.3
39[6c]	36.2	39.6	1.5
40[6c]	32.9	40.1	1.9
41[6d]	35.3	45.8	0.9

6a = PLGA-502 polymer;
6b = 10 % particle loading (2.8% hGH, 5% stearic acid);
6c = 20 % particle loading (5% hGH, 10% stearic acid);
6d = 15 % particle loading (5% hGH, 7% stearic acid).

Table 7

Formulation	PLGA RG752 (wt%)	PLGA RG755 (wt%)	BB (wt%)	BA (wt%)	EtOH (wt%)
42[7a]	48.6	-	39.8	-	-
43[7a]	48.6	-	29.8	10.0	-
44[7a]	24.3	24.3	29.8	10.0	-
45[7a]	48.6	-	35.8	-	4.0

7a = ~~5 wt%~~5 wt.% leuprolide acetate loaded.

Table 8

Formulation	PLGA RG752 (wt%)	PLC (wt%)	BB (wt%)	BA (wt%)	EtOH (wt%)
46[8a]	24.3	24.3	29.8	10.0	-
47[8a]	57.6	-	-	31.0	-
48[8a]	28.8	28.8	20.1	7.8	3.1

8a = ~~5 wt%~~5 wt.% leuprolide acetate loaded.

Table 9

Formulation	PLGA-RG752 (wt%)	PLC (wt%)	BB (wt%)
49[9a]	48.6	-	39.8
50[9a]	-	48.6	39.8

9a = ~~10 wt%~~ 10 wt.% leuprolide acetate loaded without stearic acid in the drug particle formulations.

Table 10

Formula	P(DL)LA R202 (wt%)	BB (wt%)
51[10a]	53.1	35.4
52[10a]	57.6	31.0
53[10b]	3 Month Lupron Depot®	

10a = ~~5 wt%~~ 5 wt.% leuprolide acetate loaded;
10b = 3-month Lupron Depot®

Table 11

Formulation	PLGA RG752 (wt%)	BB (wt%)	BA (wt%)
54[11a,b]	50.6	41.4	-
55[11a,b]	50.6	-	41.4
56[11a,c]	55.0	45.0	-
57[11a,c]	55.0	-	45.0

11a = ~~8 wt%~~ 8 wt.% leuprolide acetate loaded;
11b = 50 mg depot injection per rat;
11c = Placebos without leuprolide acetate

Table 12

Formulation	P(DL)LA R202 (wt%)	BB (wt%)	BA (wt%)
58[12a,b]	50.6	41.4	-
59[12a,b]	50.6	-	41.4
60[12b,c]	55.0	45.0	-
61[12b,c]	55.0	-	45.0

12a = ~~8 wt%~~ 8 wt.% leuprolide acetate loaded;
12b = 100 mg depot injection per rat;
12c = Placebos without leuprolide acetate.

Please replace paragraph number **[0175]** with the following rewritten paragraph:

Example 12

Rheological Properties ~~Of~~ of Depot Formulations

[0175] In general, viscosity of the depot vehicle formulations was tested using a Bohlin CVO 120 rheometer (Bohlin Instruments, Cranbury, NJ). All testing ~~were~~ was performed at 24° C using 20 mm parallel plates. The viscosity of various gel formulations or leuprolide acetate depot formulations of the invention, as tabulated in Tables 6-12, was tested as described above. As illustrated in Figures 1, 2 and ~~3~~ 3, the depot formulations (Formulations # 42-48, 51 and 52) have different rheological properties. Thus, the depot formulations ~~with~~ with a wide range of viscosities can be achieved by the combination of different polymers (PLGA type, molecular weight etc.), solvent or co-solvent~~;~~ and different polymer/solvent ratios according to the present invention.

Please replace paragraph number **[0176]** with the following rewritten paragraph:

Example 13

Injection force of leuprolide acetate depot formulations

[0176] The injection force of the depot vehicle formulations was tested on an Instron tensile testing instrument (Instron, Canton, MA), where the maximum force required to move the syringe plunger at a speed of 1 ml/minute was determined. The vehicle formulations were ~~pre-~~prefilled into Hamilton syringes prior to the Instron tests. All tests were conducted at room temperature, using a 24-gauge 0.5 inch long needle.

Please replace paragraph number **[0177]** with the following rewritten paragraph:

[0177] The injection force of various gel formulations or leuprolide acetate depot formulations of the invention, as tabulated in Tables 6-12, was tested as described above. As illustrated in Figures 4 and 5, the depot formulations (Formulations 42-45 and 48-50) have different injection forces. Thus, depot formulations with different injection forces can be tailored by the combination of different polymers (PLGA type, molecular weight etc.), solvent or co-solvent, ~~different~~ or different polymer/solvent ratios according to the present invention.

Please replace paragraph number **[0178]** with the following rewritten paragraph:

Example 14

In Vitro Release Rate Profiles of Depot Gel Formulations

[0178] A representative number of implantable gels were prepared in accordance with the foregoing procedures and tested for *in vitro* release of beneficial agent as a function of time. In general, the *in vitro* release of bioactive agent from the depot formulation of the present invention was performed as follows. The depot gel formulation (80-120 mg) was loaded into a tea bag and placed in a 20 mL scintillation vial and the release medium (5 mL, phosphate buffer saline (PBS) + 0.1% Tween 20, pH 7.4) was added to the vial. The vial was incubated in a 37° C water bath with gentle agitation. The medium was replaced daily for the first 5 days, then twice a week thereafter ~~till~~ until the end ~~of~~ of the release duration. The amount of bioactive agent released from the depot was measured by various methods dependent ~~the~~ on the nature of the bioactive agent: size exclusion chromatography high pressure liquid chromatography (SEC HPLC) is generally used for protein, while reverse phase high pressure liquid chromatography (rpHPLC) or ultraviolet (UV) techniques are generally used for small molecular compounds.

Please replace paragraph number **[0180]** with the following rewritten paragraph:

[0180] In general, *in vivo* studies in rats were performed following an open protocol to determine plasma levels of the beneficial agent (e.g., hGH, bupivicaine, leuprolide, buprenorphine) upon systemic administration of the beneficial agent via the implant systems of this invention. Depot gel formulations containing the beneficial agent (prepared as described in the Examples above) were loaded into 0.25 cc ~~or a~~ or 0.5 cc disposable syringes (~~e.g.~~ e.g., Hamilton Gastight syringes) or catheters. Disposable needles (16 gauge or 18 gauge) were attached to the syringes and were heated to 37° C using a circulator bath. The depot gel formulations (as tabulated in Tables 1-12) were injected into rats and blood was drawn at specified time intervals. All plasma samples were stored at 4° C prior to analysis. Samples were analyzed for the beneficial agent using any one of the following methods: radio immuno assay (RIA) or validated LC/MS/MS method (Ricerca, LLC, Painesville, Ohio).

Please replace paragraph number **[0181]** with the following rewritten paragraph:

Example 16

hGH *In Vivo* Studies

[0181] A representative number of implantable gels as tabulated in Tables 4-6 were tested for in rats to determine ~~vivo~~ *in vivo* release rate profiles as described in Example 15 above. In particular, depot gel hGH compositions were injected from customized 0.5 cc disposable syringes having disposable 16 gauge needles, into rats and blood was drawn at specified time intervals. The release rate profile of hGH from various depot gel formulations was determined by measuring the blood serum or plasma concentrations of hGH as a function of time, as illustrated in ~~Figure~~ Figures ~~6~~ 6A-D (formulations 21, 22, 29-31, and 33-40). Samples were analyzed for intact hGH content using a radio immuno assay (RIA).

Please replace paragraph number **[0182]** with the following rewritten paragraph:

Example 17

Bupivacaine *In Vivo* Studies

[0182] A representative number of implantable gels as tabulated in Table 4 were tested for in rats to determine ~~vivo~~ in vivo release rate profiles as described in Example 15 above. In particular, depot gel bupivacaine compositions were injected from customized 0.5 cc disposable syringes having disposable 18 gauge needles, into rats and blood was drawn at specified time intervals (1 hour, 4 hours and on days 1, 2, 5, 7, 9 and 14, 21 and 28) and analyzed for bupivacaine using LC/MS. Figures 7, 8 and 9 illustrate representative *in vivo* release profiles of bupivacaine hydrochloride (formulations 17 and 18) and bupivacaine base (formulations 19 and 20) obtained in rats from various depot ~~formulation,~~ formulations, including those of the present invention. The *in vivo* release profile of the depot formulations with low molecular weight PLGA (formulations 18 and 20 in Figures 7, 8 and 9) exhibited a shorter release duration of approximately 7 days, as compared to the control formulations (with higher molecular weight PLGA, formulations 17 and 19).

Please replace paragraph number **[0183]** with the following rewritten paragraph:

Example 18

Bupivacaine *In Vivo* Studies

[0183] A representative number of implantable gels as tabulated in Table 13 were tested for in rats to determine ~~vivo~~ in vivo release rate profiles as described in Example 17 above. Figures 10 and 11 illustrate representative *in vivo* release profiles of bupivacaine obtained in rats from various depot ~~formulation,~~ formulations, including those of the present invention. As illustrated in the figures, when the same amount of bupivacaine was administrated, the duration of the *in vivo* sustained release of bupivicaine from the formulation is directly proportional to the percent loading of bupivacaine within the depot gel composition. In particular, at 10% bupivicaine HCl loading, the amount of bupivicaine released increased with time after an initial decline during the first two weeks. Although not wanting to be limited to a particular theory, the

results indicate that the early stage diffusion mechanism may be the primary mechanism contributing to the release of the beneficial agent, while at later stages, polymer degradation might significantly contribute to the release.

Table 13

Formulation	PLGA RG502 (wt%)	Benzyl Benzoate (wt%)	Bupivacaine (wt%)
62	35	35	30[13a]
63	45	45	10[13a]
64	35	35	30[13b]
65	45	45	10[13b]

a = particle size of bupivacaine is ca. ~~35 μm~~ 35μm;
b = particle size of bupivacaine is ca. ~~90 μm~~ 90μm.

Please replace paragraph number **[0184]** with the following rewritten paragraph:

Example 19

In Vivo Studies on Bupivacaine Depot Composition With Different PLGA Molecular Weight Distributions

[0184] A representative number of implantable gels as tabulated in Table 2 were tested for in rats to determine ~~vivo~~ *in vivo* release rate profiles as described in Example 15 above. In particular, depot gel bupivacaine compositions were injected from customized 0.5 cc disposable syringes having disposable ~~18~~ 18-gauge needles, into rats and blood was drawn at specified time intervals (1 hour, 4 hours and on days 1, 2, 5, 7, 9 and 14, 21 and 28) and analyzed for bupivacaine using LC/MS. Figure 12 illustrates the representative *in vivo* release profiles of bupivacaine obtained in rats from the formulations 11 and 12 (the bupivacaine depots were formulated with the PLGAs with two different molecular weight distributions in benzyl benzoate (single-modal containing MMW PLGA RG502, and bi-modal mixture of HMW PLGA RG503 with LMW PLGA, Table 2 formulations 11 and 12).

Please replace paragraph number **[0185]** with the following rewritten paragraph:

Example 20

In Vivo Release Rate Profiles of

Various Leuprolide Acetate Depot Formulations

[0185] A representative number of implantable gels as tabulated in Tables 7-9 were tested for in rats to determine ~~vivo~~ in vivo release rate profiles as described in Example 15 above. In particular, ~~release~~ the release rate profile of leuprolide was determined by measuring the blood serum or plasma concentrations of leuprolide as a function of time, as illustrated in Figures 13-16.

Please replace paragraph number **[0186]** with the following rewritten paragraph:

[0186] In particular, Figure 13 illustrates representative *in vivo* release profiles of leuprolide acetate obtained in rats from depot formulations according to the present invention containing PLGA (L/G : 75/25) in either benzyl benzoate (BB) (~~formulation42~~formulation 42) or benzyl alcohol (BA) (formulation 47), as compared to a commercial 3-month leuprolide acetate depot, Lupron depot® (formulation 53). Figure 14 illustrates representative *in vivo* release profiles of leuprolide acetate obtained in rats from depot formulations according to the present invention containing PLGA (L/G : 75/25) in benzyl benzoate, ~~mixture~~ a mixture of benzyl benzoate and benzyl alcohol, or benzyl benzoate with ethanol as a thixotropic agent (formulations 42, 43 and 45, respectively). Figure 15 illustrates representative *in vivo* release profiles of leuprolide acetate obtained in rats from depot formulations according to the present invention containing PLGA (L/G : 75/25) in benzyl benzoate with the drug particles formulated either with or without stearic acid (formulations 42 & 49). Figure 16 illustrates representative *in vivo* release profiles of leuprolide acetate obtained in rats from depot formulations according to the present invention containing poly(caprolactone-co-lactic acid) (PCL-co-LA) (CL/L : 25/75) in benzyl benzoate (formulation 46) as compared to a commercial 3-month leuprolide acetate depot, Lupron depot® (formulation 53 - from TAP (The front chamber of Lupron depot® ~~3 month~~ 3-month 11.25 mg prefilled dual-chamber syringe containing leuprolide acetate (11.25 mg),

polylactic acid (99.3 mg) and D-mannitol (19.45 mg). The second chamber of diluent contains carboxymethylcellulose sodium (7.5 mg), D-mannitol (75.0 mg), polysorbate 80 (1.5 mg), water for injection, USP and glacial acetic acid, USP to control pH.)).

Please replace paragraph number **[0188]** with the following rewritten paragraph:

Example 21

In Vivo Release Rate Profiles of

Various Leuprolide Acetate Depot Formulations

[0188] A representative number of implantable gels as tabulated in Table 10 were tested for in rats to determine ~~vivo~~ in vivo release rate profiles as described in Example 15 above. In particular, ~~release~~ the release rate profile of leuprolide was determined by measuring the blood serum or plasma concentrations of leuprolide as a function of time, as illustrated in Figure 17.

Please replace paragraph number **[0189]** with the following rewritten paragraph:

[0189] In particular, Figure 17 illustrates representative *in vivo* release profiles of leuprolide acetate obtained in rats from depot formulations according to the present invention containing P(DL)LA in benzyl benzoate (BB) with different polymer/solvent ratios (~~formulation~~formulations 51 and 52), as compared to the 3 month durational depot formulation (formulation 42) and a commercial 3-month leuprolide acetate depot, Lupron depot® (formulation 53).

Please replace paragraph number **[0190]** with the following rewritten paragraph:

[0190] As illustrated in Figure 17, sustained release of leuprolide acetate from the ~~depots formulation~~ depot formulations of the invention can be achieved for a duration greater than or equal to 6 months by using the biodegradable polymer with longer degradation duration. The release profiles of the active agent from the depots can be varied by varying the type of polymer and solvent, and by varying the polymer/solvent ratios.

Please replace paragraph number **[0191]** with the following rewritten paragraph:

Example 22

InVivo Release Rate Profiles of Various ~~BuprEnorphine~~ Buprenorphine Depot Formulations

[0191] A representative number of implantable buprenorphine depot gel formulations of the present invention are tested for in rats to determine ~~vivo~~ *in vivo* release rate profiles as described in Example 15 above. In particular, ~~release~~ the release rate profile of buprenorphine is determined by measuring the blood serum or plasma concentrations of leuprolide as a function of time. The release profiles of the active agent from the depots can be varied by varying the type of polymer and solvent, and by varying the polymer/solvent ratios.

Please replace paragraph number **[0192]** with the following rewritten paragraph:

Example 23

In Vivo Testosterone Suppression by Depot Gel Leuprolide Formulations

[0192] In general, *in vivo* studies in rats were performed following an open protocol to determine plasma levels of leuprolide upon systemic administration of leuprolide via the implant systems of this invention. Depot gel leuprolide formulations (prepared as described in Examples above) were loaded into 0.25 cc Hamilton Gastight syringes. Disposable ~~18~~ 18-gauge needles were attached to the syringes and were heated to 37° C using a circulator bath. Depot gel leuprolide acetate formulations were injected into rats and blood was drawn at specified time intervals. All plasma samples were stored at 4° C prior to analysis. Samples were analyzed for leuprolide as described in Example 15 above, and for testosterone using a commercially available RIA kit (DSL-4000) (Ricerca, LLC, Painesville, Ohio).

Please replace paragraph number **[0193]** with the following rewritten paragraph:

Example 24

~~*InVivo*~~*In Vivo* Release Rate Profiles and Efficacy of

Various Leuprolide Acetate Depot Formulations

[0193] A representative number of implantable gels as tabulated in Table 11 were tested for in rats to determine ~~vivo~~ *in vivo* release rate profiles and efficacy as measured by testosterone suppression as described in Example 23 above. In particular, ~~release~~ the release rate profile of leuprolide and efficacy, ~~i.e.~~ i.e., testosterone suppression, were determined by measuring the blood serum or plasma concentrations of leuprolide and testosterone as a function of time, as illustrated in Figure 18.

Please replace paragraph number **[0195]** with the following rewritten paragraph:

Example 25

~~*InVivo*~~*In Vivo* Release Rate Profiles and Efficacy of

Various Leuprolide Acetate Depot Formulations

[0195] A representative number of implantable gels as tabulated in Table 12 were tested for in rats to determine ~~vivo~~ *in vivo* release rate profiles and efficacy as measured by testosterone suppression as described in Example 23 above. In particular, ~~release~~ the release rate profile of leuprolide and efficacy, ~~i.e.~~ i.e., testosterone suppression, were determined by measuring the blood serum or plasma concentrations of leuprolide and testosterone as a function of time, as illustrated in Figure 20.

Please replace paragraph number **[0196]** with the following rewritten paragraph:

[0196] In particular, Figure 20 illustrates representative *in vivo* sustained release profiles of leuprolide acetate obtained in rats from depot formulations according to the present invention containing P(DL)LA in either benzyl benzoate (BB) or benzyl alcohol (BA) for 6 months (formulations 58 and 59). Figure 21 illustrates the testosterone profiles of the leuprolide acetate depot formulations (formulations 58 and 59) as compared to the placebos without

leuprolide acetate (formulation 60 and 61). The leuprolide acetate depot formulations exhibited sustained release rate profiles ~~for~~ for a prolonged period of time, a duration greater than or equal to 6 months, and were efficacious in suppression of testosterone level in the rats to their castration level (<0.5 ng/mL) after 10-14 days as compared to the placebo formulations (4-5 ng/mL).